## REMARKS

Applicants wish to thank Examiner Schnizer for meeting with applicants' representative and Dr. Natarajan Sethuraman. In accordance with what was discussed during the interview, applicants provide the following remarks and request reconsideration of the present application.

After amending the claims as set forth above, claims 1-41 are pending. Claims 14-16 and 23-40 are withdrawn and claims 1-13 and 17-22 are presented for prosecution. Claims 1, 7, 17, and 21 are currently amended. The amendments made to claims 1 and 17 are discussed in more detail below. Claims 7 and 21 were amended to change the word "is" to "comprises." This amendment is not narrowing; rather, it is meant to ensure that applicants receive the broadest possible coverage. Claim 41 was added and is supported by Example 6 in the specification.

### I. The Claims are Fully Described by the Specification

Claims 1-2, 5-13, and 17-21 stand rejected under 35 U.S.C. § 112, ¶ 1, for lack of written description support. Specifically, the Examiner asserts that the specification only discloses modification of amino acids of a therapeutic agent by covalent attachment of a biocompatible polymer. As a result, applicants have amended claim 1 to recite that the therapeutic agent is covalently attached to the biocompatible polymer.

In addition, the Examiner continues to object to the use of the term "modification conditions," despite an explanation of its meaning. Accordingly, applicants have replaced the phrase "method for determining conditions for modifying" in the preamble with "method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification."

As applicants explained in their previous response, modification conditions are parameters including the type of polymer linked or joined to the therapeutic agent, the extent of modification, and the conditions of modification. *See* page 5 of the specification, lines 27-28. Applicants believe that this amendment does not change the scope of the claim, but rather

replaces the original phrase with its own definition. Similar amendments have been made to claim 17. Accordingly, applicants believe that they have overcome the written description rejection and reconsideration is respectfully requested.

**II. The Claims are Non-obvious Over the Prior Art**

The Examiner rejected claims 1-3, 5-7, 9-10, 12-13, and 17, alleging obviousness over Alvarez, *Med Pediatr Oncol.* 34(3): 200-5 (2000), in light of Graham, *Bone Marrow Transplant* 21(9): 879-85 (1998), Abshire, *Clin. Obs. Interven. Therap. Trials* 96(5): 1709-1715 (2000), and Francis, *Int. J. Hematol.* 68(1): 1-18 (1998).

Applicants submit that the cited references, read together, do not disclose all of the elements of the claimed invention. Particularly, the references do not disclose administering a second modified therapeutic agent to a subject and assaying the biological activity of the agent after the administration and after a booster does as recited in claim 1. Furthermore, the references do not disclose comparing the biological activity of a first modified therapeutic agent with a second modified therapeutic agent to select the modification conditions that prevent host-mediated inactivation of the therapeutic agent when covalently modified by the biocompatible polymer.

To ensure that the full scope of the claim is clear, applicants have amended claim 1 to replace the phrase "carrying out (1) and (2) with a second modified therapeutic agent" with the steps from (1) and (2) of assaying the biological activity of a second modified therapeutic agent after said second modified therapeutic agent has been administered to a subject and again after a booster dose. In claim 1, applicants note that the term "a subject" in element (c) includes "said subject" in elements (a) & (b) and other subjects. Indeed, claim 41 emphasizes that "a subject" in element (c) can differ from "a subject" in element (a).

In addition, applicants have revised the claim to recite expressly the selecting of the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer. This recitation was previously in the

preamble. Accordingly, applicants believe that these amendments are not narrowing but instead serve to clarify the steps that previously were present in the claim. Applicants also note that these amendments do not raise an issue of new matter and, therefore, should not necessitate further searching by the Examiner. Moreover, since they place the claims in condition for allowance, entry of these amendments is proper.

As to the non-obviousness of the amended claims, the prior art does not disclose or suggest the claimed inventions. In the past, the selection of an activated PEG and the extent of PEGylation were based on the acceptable loss of therapeutic activity and the allowable reduction in antigenicity and immunogenicity of the agent as observed *in vitro*. *See* page 2 of the specification. None of these criteria, however, take into account the effect of the host's response to the agent's biological activity after the agent is administered to the subject. Rather, they result in an arbitrary selection of activated PEG and extent of PEGylation.

The inventors discovered that over-PEGylation of an agent can disrupt the secondary and/or tertiary structure of the agent exposing it to new antigenic determinants in the immune system resulting in the agent's inactivation. *See* page 3 of the specification. Since the prior criteria do not consider these interactions, they result in a PEGylated agent that is not optimally protected from the host's immune system or other *in vivo* inactivation. Moreover, these criteria have no correlation to the ability of a subject to take the therapeutic agent over a prolonged period of time.

The claimed invention, on the other hand, takes into consideration the thermodynamics of an animal model in order to select an activated PEG and the extent of PEGylation that optimally protect the agent from the host's immune system or other *in vivo* inactivation. In addition, it takes into account the effects of the host's system over a longer period of time through the use of at least one booster step.

Turning to the examiner's reasoning for the obviousness rejection, the Examiner continues to rely on four references, Alvarez, Graham, Abshire, and Francis. The references taken as a whole, however, do not disclose each and every element of the claimed invention.

For example, the references do not disclose administering a second modified therapeutic agent to a subject and assaying the biological activity of the agent after the administration and after a booster dose. More importantly, none of the references suggests or discloses comparing the biological activity of therapeutic agents that are covalently modified with biocompatible polymers in different ways to select modification conditions that prevent host-mediated inactivation.

The examiner relies on Alvarez as disclosing studies that compare the effects of PEGylated asparaginase with native asparaginase in patients. Admittedly, however, Alvarez does not disclose a comparison between two different types of PEGylated asparaginase and it does not disclose a method comprising administering a booster dose. Additionally, Alvarez does not teach or suggest comparing the biological activity of therapeutic agents that are covalently modified with biocompatible polymers in different ways to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation.

The Examiner turns to Graham for a teaching that patients receiving PEGylated asparaginase were monitored for relapse, which the examiner asserts is an assay of a biological activity of the drug. In addition, the examiner relies on Abshire to show that PEGylated asparaginase showed prolonged half-life and reduced immunogenicity compared to native asparaginase. Again, the references do not disclose comparing the biological activity of therapeutic agents that are covalently modified with biocompatible polymers in different ways to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation. Nor do they disclose administering a second modified therapeutic agent to a subject and assaying the biological activity of the agent after administration and after a booster dose is administered.

Finally, the examiner relies on Francis to show that those skilled in the art knew that PEGylation of protein drugs can affect the bioactivity, stability, immunogenicity, and toxicity of the drugs. While Francis discloses a comparison between two different types of PEGylated asparaginase *in vitro*, it does not teach comparing the biological activity of therapeutic agents

that are covalently modified with biocompatible polymers in different ways, thereby to select modification conditions that prevent host-mediated inactivation. Therefore, the references do not disclose all of the elements of the claimed invention.

None of the references, alone or in combination, discloses administering two compositions to a subject and measuring the biological activity of the drug after each administration and after a booster step as required by the claims. Nor do any of the references disclose comparing the biological activities to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of the therapeutic agent when covalently modified by said biocompatible polymer as recited by claim 1. Moreover, the Examiner provides no motivation to combine the references in the manner suggested. Accordingly, applicants believe that claims 1-13 and 17-22 are in condition for allowance.

The Examiner rejected claim 4 as allegedly obvious over Alvarez in light of Graham, Abshire, and Francis and further in view of Petersen (US Patent No. 6,531,122). Claim 4 depends on claim 1. Therefore, for at least the reasons discussed above, claim 4 is patentable over the prior art of record.

The Examiner rejected claims 8, 11, and 20-22 as allegedly obvious over Alvarez in light of Graham, Abshire, and Francis and further in view of Roberts, *J. Gen. Virol.* 72: 299-305 (1991). Applicants note that claims 20-22 are drawn specifically to glutaminase-asparaginase. None of these references suggests using glutaminase-asparaginase and therefore these claims are patentable over the prior art. Further, claims 8, 11, and 20-22 depend on claim 1. At least the reasons discussed above, therefore, claims 8, 11, and 20-22 are patentable over the prior art of record.

The Examiner further rejected claims 18 and 19 as allegedly obvious over Alvarez in light of Graham, Abshire, and Francis and further in view of Bollin (US Patent No. 4,678,812). Claims 18 and 19 depend on claim 1. For at least the reasons discussed above, therefore, claims 18 and 19 are patentable over the prior art of record.

**III. Rejoinder of Withdrawn Claims**

Applicants respectfully request that, should the Examiner find that any of claims 1-13 and 17-22 are allowable, the Examiner also consider rejoinder of the restricted claims, and particularly the product by process claims, conditioned on their revision to conform to the allowable subject matter.

It is respectfully requested that this Amendment under 37 C.F.R. § 1.116 be entered by the Examiner, placing claims in condition for allowance. It is submitted that the proposed amendments of claims neither raise new issues nor necessitate the undertaking of any additional search by the Examiner, since all of the elements and their relationships claimed were either earlier claimed or inherent in the claims as examined. In addition, it is submitted that the amendments are presented to clarify the invention as discussed during the interview. Therefore, this Amendment should allow for immediate action by the Examiner.

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or

even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 1/12/05

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